

# Unusual Clear Cell Variant of Epithelioid Mesothelioma

Enrico Dessy, MD; Monica Falleni, MD; Paola Braidotti, DSc; Barbara Del Curto, DSc; Tiziana Panigalli, MD; Giuseppe G. Pietra, MD

● Clear cell mesothelioma is an extremely rare neoplasm of the pleura, which can easily be mistaken for a metastasis of clear cell carcinoma to the pleura. We report here the histochemical, immunohistochemical, and ultrastructural aspects of a new case of clear cell pleural mesothelioma in a 52-year-old man with no known asbestos exposure. He was admitted to the hospital for recurrent pleural effusion, which was negative for neoplastic cells at the cytologic examination. A partial decortication of the right pleura was performed. The morphologic, immunohistochemical, and ultrastructural features reported for this case are consistent with the diagnosis of clear cell mesothelioma. The differential diagnosis and immunohistochemical features in comparison with other clear cell neoplasms are discussed. (*Arch Pathol Lab Med.* 2001;125:1588–1590)

Malignant mesothelioma, a neoplasm arising from the surface serosal cells, is microscopically subdivided into epithelioid, sarcomatoid, biphasic, and “other” types on the basis of the predominant cell component.<sup>1</sup> Although epithelioid mesothelioma (characterized predominantly by a papillary or tubular growth) is the most frequent subtype, many unusual histologic variants have been described. These include adenomatoid<sup>2</sup> and deciduoid<sup>3</sup> patterns or tumors composed of small cells<sup>4</sup> or mucin-positive cells,<sup>5</sup> as well as mesothelioma with lepidic intrapulmonary growth<sup>6</sup> and others. Recently, Ordoñez et

al<sup>7</sup> described the first case of an unusual clear cell variant of pleural mesothelioma in a 74-year-old man with no history of asbestos exposure. We report here the histochemical, immunohistochemical, and ultrastructural aspects of a new case of clear cell pleural mesothelioma.

### REPORT OF A CASE

A 52-year-old man was admitted to the hospital for recurrent right-sided pleural effusions. He was a worker with no known asbestos exposure and a 40-pack-year cigarette smoker. A chest radiograph revealed a pleural effusion localized at the base of the right chest. The effusion was aspirated, but the cytologic examination failed to reveal malignant cells. A partial decortication of the right pleura was performed. The resected pleural specimens consisted of several pieces of homogeneous, thick, tan-yellow, soft tissue. The postoperative course was uneventful. The patient was well and apparently free of disease 18 months after the operation, but his condition deteriorated rapidly and he died 2 months later.

### MATERIALS AND METHODS

All the specimens were fixed in 10% neutral buffered formaldehyde solution, and 6 samples were taken at random and em-

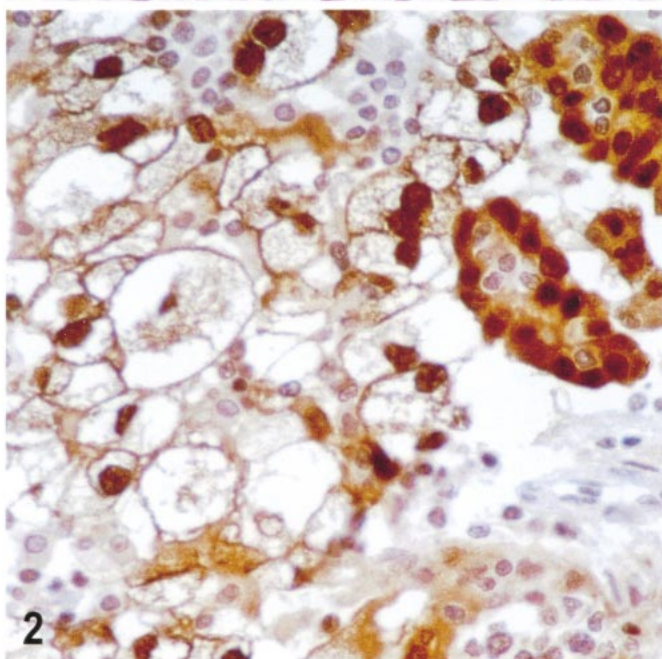
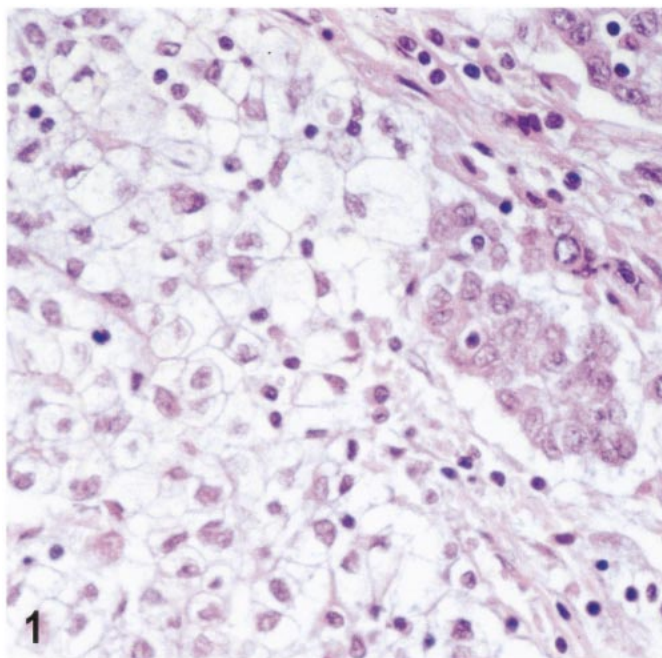
School of Medicine, University of Cagliari and Center of Oncologic Research, University of Milan, Milan, Italy (Dr Dessy); the Second Department of Pathology (Drs Falleni, Braidotti, and Del Curto) and the Department of Thoracic and General Surgery (Dr Panigalli), School of Medicine, University of Milan, Milan, Italy; and the Department of Pathology, School of Medicine, University of Pennsylvania, Philadelphia (Dr Pietra).

Reprints: Enrico Dessy, MD, Second Department of Pathology, School of Medicine, University of Milano, San Paolo Hospital, Via di Rudini, 8-20142 Milan, Italy (e-mail: anapat2@imiucca.csi.unimi.it).

Accepted for publication May 30, 2001.  
From the Department of Toxicology, Section of Molecular Pathology,

Table 1. Source and Immunoreactivity of the Antibodies

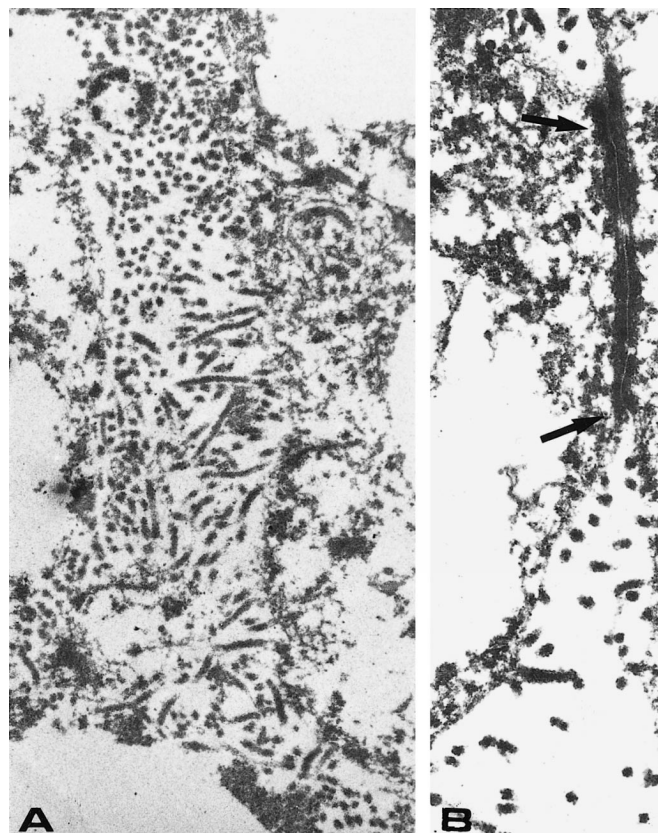
Antibody to	Clone	Source	Dilution	Reactivity
Cytokeratin 8-18	CAM 5.2	Becton Dickinson, San Jose, Calif	1:50	Cytoplasm strong in >60% cells
Epithelial membrane antigen	E29	Dakopatts, Glostrup Denmark	1:200	Membrane strong in >60% cells
Calretinin	Poly	Swant, Bellinzona, Switzerland	1:5000	Nucleus, cytoplasm, and membrane strong in >60% cells
Human mesothelial cell antigen	HBME-1	Dako	1:50	Cytoplasm and membrane strong in >60% cells
Human epithelial antigen	Ber-EP4	Dako	1:100	Negative
Carcinoembryonic antigen	Poly	Dako	1:20 000	Negative
Human pulmonary adenocarcinoma antigen	44-3A6	Affinity BioReagents, Golden, Colo	1:2	Negative
Vimentin	V9	Dako	1:1000	Negative
S100	4C 4.9	NeoMarkers, Fremont, Calif	1:2000	Negative
CD68	PG-M1	Dako	1:200	Negative



**Figure 1.** Histologic features of the tumor revealing round to polygonal epithelioid cells with clear cytoplasm and central or eccentric nuclei. Occasional papillary structures were seen among the clear cells (hematoxylin-eosin, original magnification  $\times 400$ ).

**Figure 2.** Immunohistochemistry of the tumor showing strong nuclear and cytoplasmic immunoreactivity for calretinin. Clear cells exhibit predominantly membrane immunoreactivity, whereas the cells in papillary arrangement showed strong cytoplasmic reactivity (avidin-biotin complex, original magnification  $\times 400$ ).

bedded in paraffin. Five-micrometer sections were processed for routine histology and stained with hematoxylin-eosin, periodic acid-Schiff with and without pretreatment with diastase, and Alcian blue (pH 2.5). The avidin-biotin complex immunoperoxidase technique was used on paraffin-embedded sections. Source and dilution rates of primary antibodies are shown in the Table. Negative and positive controls were added in each test. For ultrastructural investigation, samples of the tumor were retrieved from paraffin blocks, rehy-



**Figure 3.** Ultrastructural aspects of the tumor. The poor preservation of cellular features is due to retrieval from paraffin blocks. A, Neoplastic cells with numerous slender and long surface microvilli (uranyl acetate and lead citrate, original magnification  $\times 14\,000$ ). B, Higher magnification of another field showing long desmosomal junctions (arrows) between neighboring cells (uranyl acetate and lead citrate, original magnification  $\times 17\,500$ ).

drated and postfixed in buffered 1% osmium tetroxide ( $\text{OsO}_4$ ), dehydrated in ethanol, and embedded in epoxy resin.

## PATHOLOGIC FINDINGS

### Histologic Examination

The tumor was composed of large round to polygonal cells; the cells displayed abundant clear cytoplasm with evident cytoplasmic membranes and eccentric small round nuclei (Figure 1). Most cells were arranged in sheet-like structures with no evidence of either tubular or papillary patterns. Glycogen and intracytoplasmic mucins were not seen. Mitotic figures were rare ( $<1/10$  high-power fields). In many microscopic fields, the tumor cells were admixed with a marked lymphoplasmacytic infiltrate. Papillary structures lined by large cells with eosinophilic granular cytoplasm and oval-shaped central nuclei were occasionally present in 4 of 6 blocks (Figure 1). Papillary structures are characteristic of epithelioid mesothelioma and have been of help in diagnosing this unusual clear cell variant. Psammoma bodies and foci of necrosis were identified in all sections examined.

### Immunohistochemical Analysis

Tumor cells showed strong cytoplasmic staining for antikeratins, epithelial membrane antigen, calretinin (Figure 2), and HBME-1 antibodies. The complete results of the immunohistochemical panel are summarized in the Table.



### Ultrastructural Aspects

Ultrastructural examination revealed large elements with apparently empty cytoplasm. Fifty-eight percent of tumor cells showed slender and long microvilli on their free surface; however, only a few of them were cut longitudinally, allowing the careful evaluation of their length-to-width ratios (Figure 3, A). Typical long junctional complexes (large desmosomes) between neoplastic cells were identified (Figure 3, B).

### COMMENT

In 1996, Ordoñez et al<sup>7</sup> first described a case of a rare variant of epithelioid mesothelioma composed of polygonal cells with optical clear cytoplasm and no architectural arrangement in a 74-year-old man without a history of asbestos exposure. Although this case has been quoted by others in the differential diagnosis of biopsies of clear cell tumors of unknown origin involving the pleura,<sup>8,9</sup> the variant of clear cell mesothelioma has not been included in the new classification of lung and pleural tumors by the World Health Organization.<sup>1</sup> The presence of nests of clear cell elements has been reported by several authors,<sup>10</sup> but in our case and in that reported by Ordoñez et al,<sup>7</sup> the tumor was composed exclusively or predominantly of clear cells. In our case, the diagnosis of mesothelioma was based mainly on the recognition of histochemical, immunohistochemical, and ultrastructural aspects that allowed its distinction from metastatic clear cell tumors to the pleura. In the bioptic material, the histopathologic diagnosis of this variant may be difficult to make, since a variety of clear cell tumors metastasize to the pleura. Most of these tumors are represented by metastases of clear cell tumors from abdominal or thoracic organs,<sup>9</sup> which often

also involve the lung. In the present case, the neoplasm was localized exclusively in the right pleural cavity with no apparent involvement of lung parenchyma. The diagnosis was made on the basis of immunohistochemical positivity of the neoplastic cells to calretinin (cytoplasmic and nuclear), HBME-1, and epithelial membrane antigen (membrane positivity), and negativity to carcinoembryonic antigen, Ber-EP4, S100, and 44-3A6 antibodies. The diagnosis was confirmed by the ultrastructural demonstration of large desmosomes and long microvilli at the cell surface.

The authors thank Robert Rey for his technical photographic assistance.

### References

1. Travis WD, Colby TV, Corrin B, Shimosato Y, Brambilla E. *Histological Typing of Lung and Pleural Tumours*. 3rd ed. Berlin, Germany: Springer; 1999.
2. Kaplan MA, Tazelaar HD, Hayashi T, Schroer KR, Travis WD. Adenomatoid tumours of the pleura. *Am J Surg Pathol*. 1996;20:47-51.
3. Nascimento GA, Keeney GL, Fletcher CDM. Deciduoid peritoneal mesothelioma: an unusual phenotype affecting young females. *Am J Surg Pathol*. 1994;18:439-445.
4. Mayall FG, Gibbs AR. The histology and immunohistochemistry of small cell mesothelioma. *Histopathology*. 1992;20:47-51.
5. MacDougall DB, Wang SE, Zidar BL. Mucin-positive epithelial mesothelioma. *Arch Pathol Lab Med*. 1992;116:874-880.
6. Wu H, Tino G, Gannon FH, Kaiser LR, Pietra GG. Lepidic intrapulmonary growth of malignant mesothelioma presenting as recurrent hydropneumothorax. *Hum Pathol*. 1996;27:989-992.
7. Ordoñez NG, Myhre M, Mackay B. Clear cell mesothelioma. *Ultrastruct Pathol*. 1996;20:331-336.
8. Nappi O, Mills SE, Swanson PE, Wick MR. Clear cell tumors of unknown nature and origin: a systematic approach to diagnosis. *Semin Diagn Pathol*. 1997;14:164-174.
9. Gaffey MJ, Mills SE, Ritter JH. Clear cell tumors of the lower respiratory tract. *Semin Diagn Pathol*. 1997;14:222-232.
10. McCaughey WTE, Colby TV, Battifora H, et al. Diagnosis of diffuse malignant mesothelioma: experience of a US/Canadian mesothelioma panel. *Mod Pathol*. 1991;4:342-353.